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Heat shock proteins and cardiovascular disease

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The development of stress drives a host of biological responses that include the overproduction of a family of proteins named heat shock proteins (HSPs), because they were initially studied after heat exposure. HSPs are evolutionarily preserved proteins with a high degree of interspecies homology. HSPs are intracellular proteins that also have extracellular expression. The primary role of HSPs is to protect cell function by preventing irreversible protein damage and facilitating molecular traffic through intracellular pathways. However, in addition to their chaperone role, HSPs are immunodominant molecules that stimulate natural as well as disease-related immune reactivity. The latter may be a consequence of molecular mimicry, generating cross-reactivity between human HSPs and the HSPs of infectious agents. Autoimmune reactivity driven by HSPs could also be the result of enhancement of the immune response to peptides generated during cellular injury and of their role in the delivery of peptides to the major histocompatibility complex in antigen-presenting cells. In humans, HSPs have been found to participate in the pathogenesis of a large number of diseases. This review is focused on the role of HSPs in atherosclerosis and essential hypertension.

Keywords: heat shock proteins, atherosclerosis, hypertension, HSP60, HSP70, chaperones and immunity

Biology of Heat Shock Proteins (HSPs)

In 1962, Feruccio Ritossa (94) described puffiness in *Drosophila* salivary chromosomes and changes in gene expression in response to heat. This serendipitous finding was followed 12 years later by the identification of the proteins overproduced by the increase in temperature that were named HSPs (113). Subsequent studies demonstrated that the upregulation of HSP was not restricted to hyperthermia but was also induced by hypoxia, ischemia-reperfusion, energy depletion, physical stretching, acidosis, generation of reactive oxygen radicals, and in fact by just about every condition generating cellular stress (55). At present, more than 60,000 references on HSP are listed in PubMed archives.

The HSPs represent one of the most ancient and conserved proteins in prokaryotic and eukaryotic cells. They have a high interspecies homology and are constitutionally expressed

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in most cells. Their overexpression during stress has been demonstrated in every species that has been investigated, including aquatic corals, desert ants, plants, bacteria, and mammals. The HSP response to stress is so universal that it has been used as a non-specific bioindicator of pollutant contamination of the environment (116).

The transcription of the HSP gene is mediated by the interaction of heat shock elements in the gene promoter regions with the activated (phosphorylated) trimers of heat shock factors (HSFs). These HSFs are normally present in the cytoplasm as inactive monomers and when activated translocate to the nucleus. The hyperphosphorylation of inactive HSFs is induced by stressful conditions in a *ras*-dependent manner by mitogen-activated protein kinases. The family of HSFs independently or in concert regulates HSP activity driving or repressing gene activation and transcription. The human genome encodes six HSF proteins. In vertebrates, HSF1 and HSF2 are the most widely expressed HSFs. HSF1 plays the central role in the response to stress and cell survival. In contrast, HSF2 is inactivated by hyperthermia and sequestered in the cytoplasm thus avoiding interaction with the HSF1 transferred to the nucleus and may function as cancer suppressor (31).

HSPs are cytoprotective by acting as chaperones in the folding, intracellular transport, and repair of degraded proteins. In their chaperone functions, HSPs promiscuously interact with peptides ("clients") and dissociate from them once their goal is completed. The upregulation of HSPs is activated and inactivated by a fine-tuned network of transcriptional and post-transcriptional pathways and by interaction with co-chaperones that can bind simultaneously and are integrated in the management of the client peptide (31, 105).

HSPs constitute 5%–10% of the total protein content of the cells under physiological conditions and may increase up to 15% under stress (74). They are distributed in the cytoplasm, nucleus, endoplasmic reticulum, and mitochondria and because of the large number of their client molecules, the function of HSPs is not restricted to situations of cellular stress. They are critical participants in cellular homeostasis and signal transduction. In the immune response, they are involved in preservation and intracellular trafficking of antigenic peptides to the major histocompatibility complex (MHC), expression of toll-like receptors (TLRs), adhesion molecules, and production of pro-inflammatory cytokines (4, 28, 54, 81, 83, 90, 92, 105, 115). While the results of many studies have given support to the roles of HSPs stimulating immunity and inflammation, it is impossible at times to separate the effects of the HSP itself from its association with contaminating agents, in particular, endotoxin originated in the bacteria used for HSP extraction. As will be discussed later, the findings of HSP70-induced production of cytokines and its binding to the MHC in antigen-presenting cells (APCs) are abrogated when endotoxin-free HSPs are used (9, 29).

HSPs are classified by their molecular weight and are grouped in families (45, 134). The most important HSPs in human diseases are:

– *Small HSP (sHSP) group.* These HSPs have a small size (16–40 kDa) and are present in the cytoplasm and the nucleus. They include HSP27 (HSPB1), heme oxygenase (HSP32), αB-crystallin (HSPB5), and αA-crystallin (HSPB4). sHSPs function as cytoskeleton stabilizers and some have antioxidant properties (HSP32) of central importance in some disease states. sHSPs prevent the irreversible aggregation of damaged proteins in an ATP-independent manner and transfer damaged proteins to ATP-dependent chaperones, for example, HSP70. Members of this family inhibit specific stages of some apoptotic pathways. Numerous studies have uncovered protective role of HSP27 in atherosclerosis.

- *HSP40.* HSP40 is a member of the DnaJ family that comprises the largest number of HSPs in humans. This family presents a J-domain responsible for recruitment of members of the HSPA family (includes HSP70) and stimulation of ATPase activity and thus regulates the activity of other co-chaperones. HSP40 promotes rearrangement of proteins by successive folding and refolding of protein aggregates and facilitates collagen preservation and transport of collagen.
- *HSP60.* This chaperonin family includes HSP60 in mammals and mycobacterial HSP65, chlamydial HSP60, and *Escherichia coli* GroEL homologues. HSP60 is present in the cytoplasm, mitochondria, endoplasmic reticulum, and nucleus. HSP60 binds to partially folded polypeptides, prevents their aggregation, and assists the development of correct refolding. HSP60 is released from cells after necrosis and is an important signal of cell death. The role of HSP60 in atherosclerosis, rheumatoid arthritis, diabetes mellitus, and neurological diseases has extensively been studied.
- *HSP70.* HSP70 and other members of the HSPA family have an N-terminal ATPase domain and a C-terminal domain that bind hydrophobic regions in polypeptides and by repeated folding and refolding avoids the exposure and aggregation of polypeptide clients. The chaperone function of HSP70 involves the participation of co-chaperones and is involved in a multitude of protein interactions. HSP70 family members may facilitate DNA repair and play a role in the transfer of the client peptides across membranes. HSP70 has been implicated in the pathogenesis of atherosclerosis and as an autoantigen in the pathogenesis of hypertension.
- *HSP90.* HSP90 is a member of the HSPC family. It has an ATP-binding amino terminal domain, a middle domain for binding with clients and a carboxyterminal domain, responsible for dimerization and interaction with co-chaperones. Humans have two HSP90 genes: HSPα that is constitutively expressed and HSPβ that is heat-induced (105). HSP90 recognizes and binds denatured proteins preventing irreversible aggregation and cooperates with members of the HSPA family facilitating nucleotide exchange. In addition, HSP90 binds to specific glucocorticoid receptors. Deletion of HSP90 allows the expression of normally suppressed phenotypes, which raises the possibility of HSP90 could play a role in suppressing detrimental spontaneous mutations (43, 102). It plays a role in the pathogenesis of atherosclerosis and systemic lupus erythematosus.

Characteristics of HSPs relevant to autoimmune disease

While HSPs are primarily cytoprotective as described earlier, they are immunodominant molecules with several characteristics that may stimulate autoimmune reactivity. One of these characteristics is the highly preserved interspecies homology. The similarity of HSPs across species carries the potential of cross-immune reactivity between the HSPs in invading microorganisms and the corresponding HSPs in the host and thereby may cause unintentional autoimmune responses directed to human HSPs. A number of investigations have made use of the homologies between human HSP60 and *E. coli* GroEL, *Mycobacterium tuberculosis* HSP65, *Chlamydia trachomatis* HSP60 GroEL-like and HSP60 of *Candida*, *Aspergillus*, and *Histoplasma* (47, 69, 104, 108, 117, 128). Similar homologies between human HSP70 and the HSP70 in *M. tuberculosis and Mycobacterium leprae*, *Candida*, *Aspergillus*, and *Histoplasma*, and DnaK-like HSP70 of *C. trachomatis* have been the bases of important investigations (42, 69, 104, 107, 119, 125). In fact, molecular mimicry is used in the design of therapeutic strategies that induce regulatory T cell (Treg) responses in the host by administration of specific peptide sequences of bacterial HSPs (120).

In addition to molecular mimicry, it has been postulated that HSPs can stimulate immunity against peptides generated during cellular injury because of their capacity to enhance immune reactivity directed to other antigens. This characteristic is the reason to incorporate HSP to vaccines directed against specific cancers (17). Finally, HSPs have also been assigned a critical role in facilitating the traffic of extracellular and intracellular peptides to MHC types I and II in APCs by canonical and cross-presentation pathways (39, 40, 138). However, some studies have questioned the direct stimulatory effects of HSPs on immune reactivity to other peptides. Careful studies have demonstrated that HSP70 contamination with endotoxin is responsible for the generation of tumor necrosis factor from macrophages (29) and endotoxin contamination is also responsible for HSP70 activation of APCs (9). Furthermore, it has been reported that the immunostimulatory properties of HSP70-antigen fusions are lost after endotoxin depletion (66). Therefore, some pro-inflammatory and immune stimulatory functions of HSPs may require the association with other components; in fact, HSP vaccines prepared with therapeutic purposes are prepared in association with other peptides (32, 50).

In addition to the role of HSPs in stimulating autoimmunity in disease conditions, HSPs are emerging as a central player in natural autoimmunity. Antibodies against HSPs, particularly HSP60, are detected in the umbilical cord blood, maintain long-term stable levels, and are independent of infection (121). Therefore, natural autoantibodies of HSPs are part of a normal immune system (72, 118). The role of natural autoantibodies is a subject of debate and it has been proposed that they have a protective function. Disease-related HSP immune reactivity would result from changes in phenotypes of natural autoantibodies or by increase above a certain threshold as a consequence of environmental (repeated infections) or genetic factors (20).

Another aspect relevant to the autoantigenic potential of HSPs is their possible extracellular localization. Although HSPs are intracellular proteins, their extracellular location is critical for their capacity to trigger HSP-directed autoimmune reactivity. HSPs or HSP-protein complexes may escape to extracellular locations by passive leakage during necrosis as well as by several mechanisms unrelated to cell damage. HSPs may be engulfed inside cell membranes and released in ectosomes and exosomes from cells in the peripheral circulation. The ectosomal location of HSPs has been demonstrated for HSP27, HSP70, HSP60, and HSP90 (8, 16, 34, 57). In addition, HSPs may be extruded from the cells in association with lysosomes. In support of this mechanism is the finding that HSP70 has been identified in association with lysosomal proteins (65). Finally, it is possible but presently unproven that direct protein translocation of HSPs may take place through interaction with lipids in cell membranes, as has been shown to occur for fibroblast growth factor-2 (79). In specific circumstances, both passive leakage and active secretion may be responsible for the extracellular presence of HSPs (64). Any of these mechanisms may be responsible for the existence of circulating levels of HSP and anti-HSP70 in normal individuals (84, 86, 110).

In humans, the role of HSP has been studied in a large number of unrelated conditions and diseases, including aging, cancer, transplantation, atherosclerosis, hypertension, Alzheimer's disease, diabetes, arthritis, multiple sclerosis, asthma, neurodegeneration (Huntington's chorea and Parkinson's disease), cerebral and myocardial ischemia, heat-stress associated nephropathy, and immunity to infectious agents. The present review will focus on the role played by HSP in the pathogenesis of atherosclerosis and essential hypertension.

HSPs and Atherosclerosis

Atherosclerosis is a disease characterized by deposition of lipids, particularly low-density lipoproteins (LDLs) in the intimal layer of large- and medium-sized arteries in association with infiltration of immune cells and remodeling of arterial walls. The lipid composition of the plaques and the infiltration of mononuclear cells were described almost two centuries ago (71), but the important role of inflammation in the pathogenesis of the disease has been recognized only in the past three to four decades (100).

The critical role of immune reactivity in atherosclerosis was originally elucidated by studies that examined the results of treatment with immunosuppressive agents. Using a model of high fat diet-induced atherosclerosis in rabbits, our group (99) and others (33, 123) showed that treatment with the immunosuppressive agent, mycophenolate mofetil, markedly prevented plaque formation, infiltration of inflammatory cells, and the proliferation of vascular smooth muscle cells in the aorta (Fig. 1). Importantly, the reduction of the infiltration of immune cells was also associated with a reduction in the lipid (cholesterol) content in the vessel walls, thereby underlining a role of local inflammation in the formation of the atherosclerotic plaque. The notion that atherosclerosis is an autoimmune disease was advanced by Wick et al. (129) and the knowledge that oxidized LDL is toxic for endothelial cells prompted research on the nature of the immune reactivity induced by oxidized LDL and the proliferation of smooth muscle cells in arterial walls (78). In recent years, significant insight has been gained on the involvement of the innate and adaptive immune reactivity in atherosclerosis and on the role played by HSPs in the pathogenesis of the disease (129).

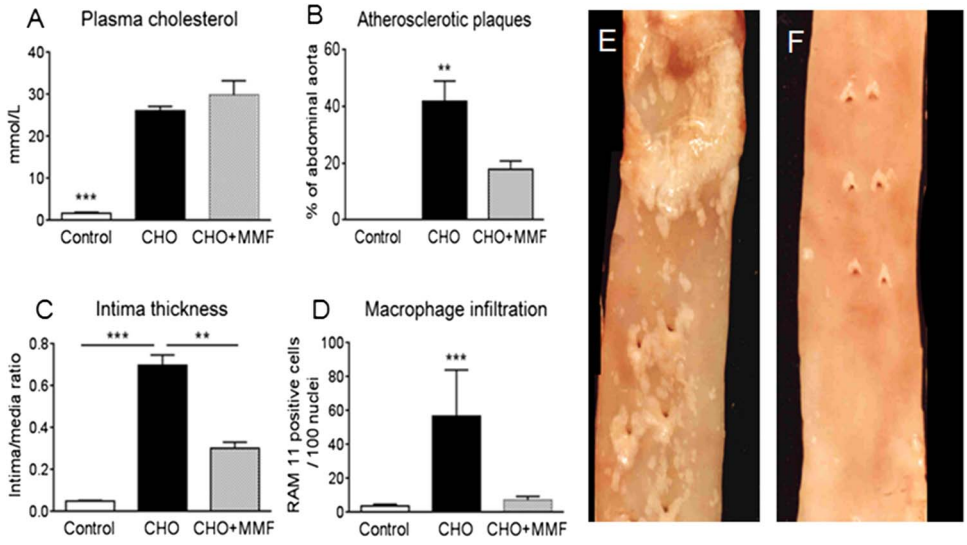

Fig. 1. Effect of immune suppression with mycophenolate mofetil (MMF, 30 mg/kg daily) on atherosclerosis induced in rabbits by the ingestion of 1% cholesterol diet (CHO) for 12 weeks. (A) No difference was detected in the plasma cholesterol between the CHO and CHO + MMF groups ($n = 10$ in each group). However, there was a reduction of more than 50% atherosclerosis in the aorta (B and C) and an eightfold reduction in macrophage infiltration (D). Abdominal aortic in CHO group (E) shows extensive atherosclerosis plaques that were not present in the CHO + MMF groups (F). Figure made using data from (99). $^{**}p < 0.01$. $^{***}p < 0.001$

The atherosclerosis lesion

The initial lesions in atherosclerosis are fatty streaks in the intima (Fig. 2). Oxidized LDLs (oxLDL) act as danger-associated molecular patterns (DAMPs) that stimulate innate immunity, generating autoantigens that engage the adaptive immune response. Local inflammation is modulated by participation of Treg responses (111). Even in the early stages of fatty deposition, there is a cellular component in the lesion, consisting of foam cells, macrophages, and T cells. B lymphocytes are more prominent in the adventitial layer of the arteries. The lesion evolves to the formation of plaques that may be stable and covered by a fibrous cap. Growth and rupture of the plaque and remodeling of the arterial wall result from active inflammation driven by the production of pro-inflammatory cytokines and prothrombotic mediators.

The immune system in atherosclerosis

Innate and adaptive immunity triggered by the generation of lipid peroxidation products drives the inflammatory lesion in atherosclerosis (11, 38). The critical role of the innate immune response in the pathogenesis of atherosclerosis has been underlined by the studies of Ridker et al. (93) who showed a reduction in the recurrent cardiovascular-related death,

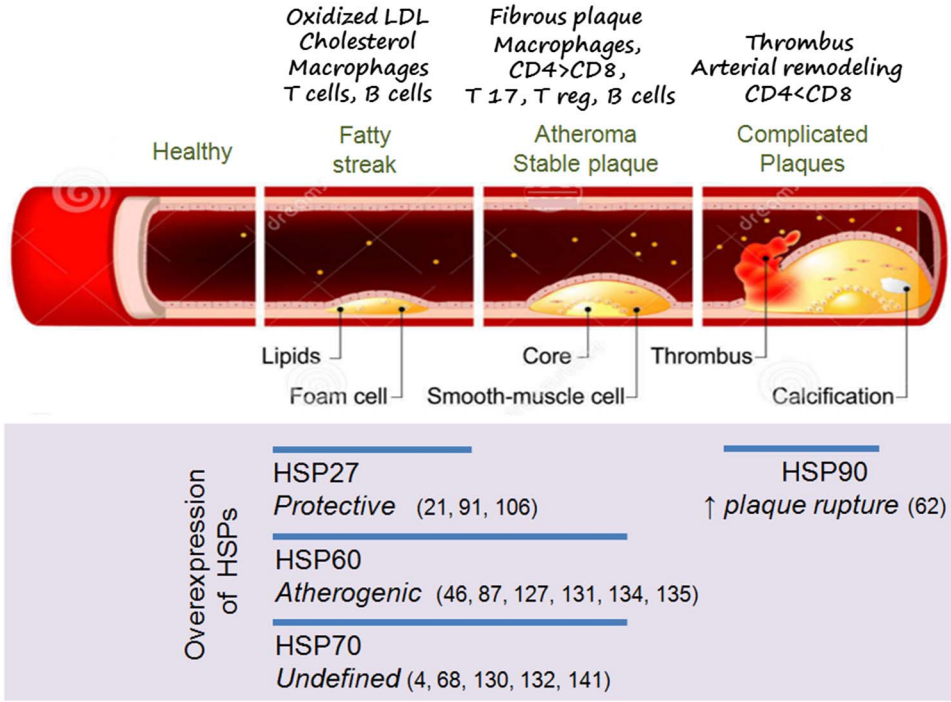

Fig. 2. The role of HSP in the pathogenesis of atherosclerosis. Available evidence suggests that overexpression of HSP27 is protective, whereas overexpression of HSP60 is atherogenic. The effects of HSP70 are inconclusive and HSP90 aggravates and complicates atheroma. Conflicting evidence exists in relation to associations between HSP levels and severity of atherosclerosis (Table I). Induction of regulatory T cell responses with HSP60 and derived peptides improves experimental atherosclerosis. The stages of atherosclerosis were modified from images in Dreamsite.com. Numbers in parenthesis indicate the corresponding references

myocardial infarction and stroke, independent of lipid lowering, with the treatment with a monoclonal antibody targeting interleukin (IL)-1β. Strong evidence also supports the participation of adaptive immunity in the progression of atherosclerosis as oxidized lipoproteins generate the production of Th1 cytokines, a process that is suppressed by the Th2 cytokine IL-5 (12).

In human plaques, 70% of T cells are CD4+ T cells and almost all remaining cells are CD8+ T cells (44). Tregs, Th17 cells, and natural killer cells are also present, but in lesser numbers, in atherosclerotic lesions (48, 49). In later stages, tertiary lymphoid organs containing a variety of T-cell types and B cells are formed in the arterial adventitia (76). The role of T-cell subtypes has extensively been studied. CD4+ T cells aggravate atherosclerosis (139, 140). The Th1 subtype of CD4+ T cells is pro-inflammatory and proatherogenic (15, 35), whereas the Th2 subtype has been found both to protect (12) as well as to aggravate (23, 51) atherosclerosis. Tregs are atheroprotective (1). Conflicting reports indicate that IL-17 may attenuate (22, 112) or worsen (26, 30, 109) atherosclerosis. Infiltrating CD8+ cytotoxic T cells favors plaque instability and rupture (56) and natural killer T cells have been found to be proatherogenic in early stages of the disease (5).

The role of B cells in atherosclerosis remains controversial, with some studies indicating protection, whereas others suggesting acceleration of the disease (49).

HSPs in atherosclerosis

The most extensively studied HSPs in atherosclerosis are HSP27, HSP60, HSP70, and HSP90. Specific findings and the experimental models used in several investigations are shown in Table I. The protective and atherogenic potential of overexpression of these HSPs are summarized in Fig. 2.

HSP27. The intracellular chaperone function of HSP27 is regulated by phosphorylation and dephosphorylation in large aggregates that modulate the assembly of an ATP-independent network (6). As a chaperone, HSP27 plays a role in RNA stabilization, supports antioxidant responses, and is antiapoptotic (8). Extracellular release from atherosclerotic tissue may result from cellular injury or occur in association with secretory lysosomes or exosomes. In the extracellular location, HSP27 binds to a number of cell membrane receptors in endothelial cells and immune cells, including CD91, CD40, CD36, CD14, scavenger receptor A (SR-A), and TLRs: including TLR2, TLR3, and TLR4 (11). Recombinant HSP27 induces TLR-mediated activation of NFκB with the secretion of pro-inflammatory as well as the anti-inflammatory (IL-10 cytokines) (103). In atherosclerosis, available evidence supports the notion that HSP27 offers protection against the progression of the disease. In fact, the identification of HSP27 as an estrogen receptor-associated protein is likely the reason for the apparently protective role of estrogens in atherosclerosis (75, 91). Atherosclerotic plaques have lower HSP27 content (67), lower circulating levels of HSP27 are associated with more severe atherosclerotic disease (106), and HSP27 overexpression protects mice from atherosclerosis (21). Potential mechanisms involved in the anti-atherogenic activity of HSP27 include the suppression of NFκB activation by intracellular HSP27 (8) and the possible participation of HSP27 in lipid homeostasis, since it competes with LDL binding to SR-A, attenuates foam cell formation (8), and reduces the cholesterol content in the serum and atherosclerotic plaques (21).

HSP60. Endothelial cells express HSP60 under a variety of stressful conditions. In addition, the cross-reactivity between bacterial and human HSP60 may be responsible for the development of a harmful autoimmune reactivity that may be an undesirable consequence

Table I. Selected studies that offer insight on the role of HSPs in atherosclerosis

HSP	Experimental model	Findings	References
HSP27	Cell culture	Increased activation of NFκB macrophages and production of pro- and anti-inflammatory cytokines	(103) (Φ)
	Patients	Low plasma HSP27 levels associated with coronary artery stenosis	(106)
	(*) ApoE$^{-/-}$ mice overexpressing HSP27	Reduced *de novo* atherosclerosis and increased plaque stability	(106)
	Patients (endo-atherectomy and serum samples)	Low HSP27 in atherosclerotic plaques and low serum levels in patients with atherosclerosis	(68)
	ApoE$^{-/-}$HSP27 (**) mice	Inverse correlation between lesion area and HSP27 levels. Reduction of IL-1β and increase in IL-10 in mice overexpressing HSP27	(91)
	ApoE$^{-/-}$HSP27 (**) mice	Chronic overexpression of HSP27 reduces lesions and arterial remodeling	(21)
HSP60	ApoE$^{-/-}$mice	HSP60 (and HSP70) overexpression precedes inflammation	(46)
	Review of several experimental models	Adoptive transfer of T cells reactive to HSP60 induces atherosclerosis. Tolerization with HSP60-derived peptide arrests atherosclerosis	(127)
	Patients	Serum HSP60 and anti-HSP60 levels correlate with atherosclerosis, anti-lipopolysaccharide, and various markers of inflammation	(87, 131, 133, 135)
HSP70	Patients	Inverse relationship between HSP70 levels and severity of atherosclerosis	(68, 141)
	Patients	High plasma HSP70 levels and anti-HSP70 in peripheral vascular disease	(130)
	SD rats	Elevation of plasma HSP70 precedes diet-induced atherosclerosis	(132)
	Cell cultures	HSP70 bound to plasma membrane activates NFκB and upregulates the expression of pro-inflammatory cytokines by CD4- and Ca-dependent pathways	(4) (Φ)
HSP90	Atherosclerotic plaques human and mice	HSP90 immunostaining was increased in inflammatory regions of plaques, inhibition of HSP90 attenuates inflammation in atheromas	(62)

*HSP27 overproduction in the apolipoprotein E $^{-/-}$ (ApoE$^{-/-}$) atheroprone mice induced by transplantation of bone marrow overexpressing HSP27.
**The apoE$^{-/-}$HSP27 mice are a cross-bred product of ApoE$^{-/-}$ mice and mice overexpressing HSP27. SD: Sprague–Dawley. Φ indicates studies using recombinant HSP purified and analyzed for potential contamination with endotoxin

of a preexisting protective immunity to an infectious agent (54, 127, 128). HSP60 has a direct atherogenic potential and the accumulated evidence supports the notion that HSP60-reactive T cells initiate atherosclerosis and the antibodies directed to HSP60 drive the chronicity of the disease (Fig. 2). In human atherosclerosis, several HSP60 epitopes have been found to have T and B cell cross-reactivity with bacterial HSP60 (128). Experimental studies have shown that upregulation of HSP60 expression precedes the development of atherosclerotic lesions (46) and genetically normocholesterolemic mice develop atherosclerotic lesions if immunized with HSP60; furthermore, adoptive transfer of HSP60 reactive T cells induces early (fatty streaks) atherosclerosis (127). In humans, high-circulating levels of HSP60 and anti-HSP60 are correlated with atherosclerotic cardiovascular disease (87, 133, 135), carotid artery wall thickness (131, 133), and atherosclerosis-related morbidity and mortality (136). Specific T-cell immunity to HSP60 exists in the early stages of atherosclerosis (53) and T cells obtained from human atherosclerotic lesions show cross-reactivity with bacterial (mycobacterium and chlamydia) HSP sequences (2).

While contamination with endotoxin was not rigorously excluded in all studies, it has been shown that HSP60 administration could promote or suppress atherosclerosis depending on route of administration, the type of APCs, and the co-stimulatory molecules involved. The parenteral route of HSP60 administration induces adhesion molecules and infiltration of HSP60-specific T cells that are followed by secretion of pro-inflammatory mediators and anti-HSP60 antibodies, invasion of macrophages, lipid deposition, and the formation of atherosclerotic plaques. The oral or nasal route of administration of HSP60 (or HPS60-derived peptide sequences cross-reactive with *M. tuberculosis*) induces tolerance. Tolerance develops as a consequence of the generation of Tregs and anti-inflammatory mediators (IL-10 and transforming growth factor beta) and results in reduced atherosclerotic lesions (127). The induction of oxLDL-reactive Tregs also reduces plaque formation and when peptide sequences of human apolipoprotein B, human HSP60, and *Chlamydophila pneumoniae* were used in combination, a synergistic atheroprotection was found (61). As noted by Wick (127), the tolerization strategies are based on the use of peptide sequences with high homology to self that, nevertheless, are immunogenic. Protective vaccines against atherosclerosis using peptides derived from ApoB100, HSP60, and a combination of their epitopes are being actively investigated at present (32).

HSP70. HSP70 is found in the atherosclerotic plaques and is overexpressed in advanced lesions. HSP70 attenuates the activation of NFκB, which would suggest anti-inflammatory activity (134); however, there are conflicting reports that preclude assigning HSP70 a definite role in atherosclerosis at present (Fig. 2). Plasma levels of HSP70 have been found to have an inverse (68, 141) as well as a direct (130, 132) association with the severity of atherosclerosis. HSP70 administration has been found to induce production of IL-6 (pro-inflammatory) (4) as well as Treg (anti-inflammatory) response (125). A high-cholesterol diet has been shown to increase HSP70 plasma levels and exogenous HSP70 induced overexpression of adhesion molecules in peripheral blood mononuclear cells. These results suggest that HSP70 favors infiltration of mononuclear cells and atherosclerosis (132). In contrast, studies investigating the inhibition of HSP90 activity (62) have found that the observed reduction of inflammation and oxidative stress in arterial walls was associated with increased expression of HSP70 and suggested protective effects of HSP70 stimulation. The pro- and anti-atherogenic effects of HSP70 are presently a matter of debate (10).

HSP90. Work on HSP90 has principally centered in cancer. Several studies have explored its role in atherosclerosis, where overexpression of HSP90 is associated with features of plaque

instability. Inhibition of HSP90 has resulted in a reduction in inflammation and in oxidative stress resulting from reduced activation of transcription factors (signal transducers and activators of transcription and NFκB) and suppression of pro-inflammatory cytokines. Interestingly, the beneficial effects of suppressing HSP90 activation are associated with overexpression of HSP70 that is assumed to contribute to an overall anti-inflammatory and atheroprotective activity of HSP90 inhibition (62).

HSPs in hypertension

The hypertensive condition

Blood pressure is a biological variable with normal distribution and the definition of hypertension is arbitrary and related to the risk that is attributed to progressively higher values. Hypertension (blood pressure ≥140/90 mmHg) is the most important contributor to the global burden of disease and causes 9.4 million deaths every year; furthermore, the worldwide prevalence of hypertension is predicted to increase 10% between 2000 and 2025 (60). Hypertension is classified as secondary when there is a clear etiologic factor and primary (essential) when a well-defined cause of high blood pressure is not apparent and hereditary and environmental influences play a pathogenic role. More than 65 genetic loci have been found in association with high blood pressure, yet, most of them correspond to genes not usually related to blood pressure homeostasis and the combination of genetic characteristics has been estimated to explain no more than 3% of the hereditability of hypertension (77). Putative causes of essential hypertension include lower birth weight resulting from maternal malnutrition (137) and epigenetic modification of genes (59). The importance of the ambulatory blood pressure determinations, the risks apparently imposed by blood pressure variability, the recommended treatment approaches, and the guidelines for blood pressure control have recently been reviewed (89).

The ability of a high salt diet to increase blood pressure has been recognized for many years (13, 36) and the concept of salt sensitivity refers to an increase in blood pressure resulting from changes in standardized low and high salt administration that exceed "normal" variation (124). Salt sensitivity increases with age and arterial rigidity. While hypertension was classically viewed as strictly a hemodynamic disorder, increasing evidence has showed that hypertension is driven, at least in part, by inflammation in the kidneys (suppressing pressure natriuresis), in the arterial walls (impairing endothelial vasodilatation), and in the central nervous system (stimulating the sympathetic outflow) (96, 97).

Autoimmunity in the pathogenesis of hypertension

The immune cell infiltration in the kidney in salt-sensitive hypertension consists of both T cells and macrophages. Evidence that these cells have a role in hypertension has been shown in experimental models that evaluated the changes in blood pressure resulting from depleting specific cell populations. Using this approach, there is evidence for a prohypertensive role of macrophage infiltration (18, 24, 126), CD4 and CD8 T cells (37, 70, 101, 114), T17 cells (3, 80), and B cells (19), as well as the anti-hypertensive role of Tregs (7, 63, 73).

It has been postulated that the inflammatory response may be initiated by local injury induced by renal vasoconstriction, resulting in ischemia that stimulates release of DAMPs that activate the innate immune response, followed by the exposure of specific endogenous antigens that trigger an adaptive immune response (95–97).

In hypertension, HSP70 as well as isoketal-modified proteins may represent endogenous antigens of importance in the pathogenesis of high blood pressure (Fig. 3).

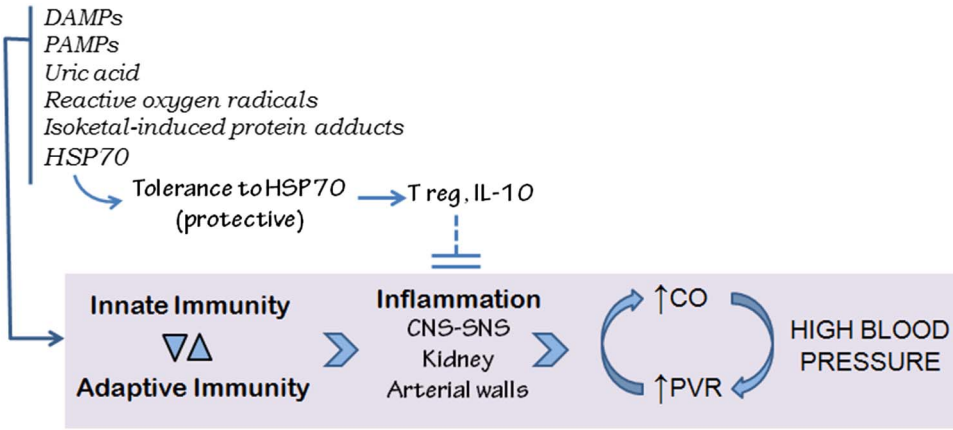

Fig. 3. HSP70 is a relevant endogenous antigen in essential hypertension. Inflammation resulting from innate and adaptive autoimmunity induces and sustains hypertension. Experimental induction of tolerance to HSP70 results in the generation of IL-10-driven regulatory T cell response that prevents inflammation and salt-induced hypertension (88). DAMPs: danger-associated molecular patterns; PAMPs: pathogen-associated molecular patterns; CNS: central nervous system; SNS: sympathetic nervous system; CO: cardiac output; PVR: peripheral vascular resistance

Isoketal-modified proteins. Studies in several experimental models by David Harrison and co-workers indicate that γ-ketoaldehydes (isolevuglandins or isoketals) resulting from oxidation of lipoproteins bind to lysine residues in proteins and generate protein adducts that represent autoantigens of pathogenic relevance in hypertension. These isoketal-modified proteins have been found to stimulate T-cell activation (52), and to participate in the co-stimulatory process of antigen recognition (122) and in the generation of memory cells (41).

In humans with hypertension, the isoketal-protein adduct content of mononuclear cells, CD14+ cells and CD18+ dendritic cells in peripheral blood is several-fold higher than in normotensive controls and the number of isoketal-positive CD14+ and CD83+ cells correlate with the degree of hypertension (52).

HSP70. Another autoantigen with potential participation in the pathogenesis of hypertension is HSP70 (98). In support of this possibility, we found that renal overabundance of HSP70 (but not other HSPs), circulating anti-HSP70 antibody titers and T-cells reactive to HSP70 were present in several experimental models of hypertension (14, 82, 95). Subsequent studies were conducted in the model of salt-induced hypertension that follows transient inhibition of nitric oxide synthase. In this model, T cells present a clonal CD4 response to HSP70 and the intraperitoneal injection of a highly preserved amino acid sequence of *M. tuberculosis* HSP70 resulted in the generation of IL-10-producing Tregs and prevention of hypertension. In addition, adoptive transfer of T cells isolated from the spleen of tolerized rats reversed hypertension. Furthermore, HSP70 gene delivery to the kidney of rats sensitized to HSP70 was associated with increment in blood pressure in response to a high salt diet (88). Several groups, including ourselves, have reported increased circulating anti-HSP70 antibody titers in patients with essential hypertension (27, 85, 88, 110). Hypertensive patients have also increased HSP70 gene expression and HSP70 protein abundance in circulating leukocytes (110) and, in a limited number of patients, we showed that T cells from patients with essential hypertension responded to a challenge with HSP70 with a strong proliferative reaction (88). Li et al. (58) have reported that certain HSP70 gene haplotypes (H5 and H8) are associated

with hypertension in the Uygur ethnic minority in China and genome wide association studies have identified single nucleotide polymorphisms of HSPs in the BAT2-BAT5 loci (HSPA1L, HSPA1A, and HSP1B) associated with hypertension (25).

The induction of tolerance to HSP70 has not been evaluated as a therapeutic strategy in patients with essential hypertension. The lack of significant side effects associated with oral HSP60 and derived peptides in clinical trials of prevention of atherosclerosis (32, 50, 128) suggests that a similar approach could be investigated for the treatment of essential hypertension. Future studies on the participation of HSP-driven autoimmunity may bring important insights on the pathogenesis and hopefully treatment of essential hypertension.

Acknowledgements

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Conflict of interest

BR-I has no conflict of interest. RJJ is on the Scientific Board of XORT Therapeutics and has patent and patent applications related to lowering uric acid or blocking fructose metabolism in the treatment of hypertension and metabolic disorders.

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